Clostridium botulinum toxin is selected from the group consisting of Type B toxin and Type E toxin.

30. (New) The composition of Claim 29, wherein said non-toxin protein sequence comprises a poly-histidine tract.

31. (New) The composition of Claim 29, wherein said vaccine is substantially endotoxin-free.

REMARKS

Claims 10-14 and 25-28 are at issue and have been rejected by the Examiner in the present Application. For clarity, the rejections at issue are set forth by number in the order they are herein addressed:

(1) Claims 10-14 and 25-28 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious; and

(2) Claim 14 stands rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

Applicants believe the present amendments and following remarks traverse the Examiner's rejections of the Claims.

I. A *Prima Facie* Case of Obviousness is Not Established For Claims 10-14 and 25-28.

The Examiner has rejected Claims 10-14 and 25-28 under 35 U.S.C. §103(a) as allegedly being unpatentable over Thompson *et al.*, Eur. J. Biochem. 189: 73-81 [1990], in view of Binz *et al.*, J. Biol. Chem. 265: 9153-58 [19990], Roitt, Essential Immunology, Sixth Ed., Blackwell Scientific Publications, Boston, MA, p. 173-178 [1988], LeClerc *et al.*, J. Immunol. 144(8): 3174-82 [1990], Kleid, Annals NY Acad. Sci. 413:23-30 [1980], Siegel, J. Clin. Microbiol. 26: 2351-56 [1988], and Ford *et al.*, Protein Expression and Purification 2: 95-107 [1991]. Applicants respectfully traverse this rejection.

The combination of references referred to by the Examiner fails to provide a *prima facie* showing of obviousness as required by §2143 of the Manual of Patent Examining Procedure (MPEP). There are three criteria which must be met to provide *prima facie* obviousness: the first requirement is that there is a suggestion or motivation in the references

or the knowledge generally available to combine the reference teachings; second, the prior art must teach or suggest all the claim limitations; and third, there must be a reasonable expectation of success, should the combination be carried out. Applicants submit that the Examiner has failed to set forth a *prima facie* case of obviousness because none of three elements have been met.

A. No Motivation to Combine References

When applying 35 U.S.C. §103, the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n. 5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants note that the purpose behind the motivation to combine requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent decision, articulates this position:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *See In re Rouffet et al.*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998).

The references do not suggest the desirability of making the combination. In the Office Action dated 2/18/98, the arguments of which the Examiner relies upon, the Examiner stated that one of ordinary skill in the art would be motivated to combine the references because "[i]t is well known that recombinant fusion proteins offer the advantage of large scale production, the possibilities of altering "native" protein to incorporate desirable characteristics (for vaccines, an example would be addition of highly immunogenic epitopes), and advantages for purification (the addition of "tags" to facilitate purification has been well known in the art)."

Applicants note that the Claims specify that the vaccine is "soluble and neutralizing." Nowhere in the present or past Office Actions does the Examiner "show reasons" why one skilled in the art would expect the *Clostridium botulinum* toxin fusion proteins of the present invention to be soluble when prior *Clostridium botulinum* toxin fusion proteins were not

soluble. The Examiner is apparently relying on some mythical high level of skill in the art. Such unsupported statements are exactly what the *Rouffet* court sought to prevent. The Federal Circuit stated:

> The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. *Rouffet*, 47 USPQ2d at 1458.

Contrary to the Examiner's opinion, the prior art provides no motivation to combine the references to teach the claimed invention of a soluble vaccine comprised of *Clostridium botulinum* toxin fusion proteins. The Examiner cannot simply invoke the fact that some properties of fusion proteins are well known, he must meet the Rouffet standard of "showing reasons" why there is a motivation to combine to achieve solubility. Because the Examiner has not "shown reasons" why there is a motivation to combine the references, a *prima facie* case of obviousness has not been established. Accordingly, the Claims should be passed to allowance.

B. The Combined References Do Not Teach Each Element of the Claims

Even if the references are properly combined, and Applicants contend that they are not, the references do not teach each element of the Claims. In reversing a determination of obviousness by the Board of Patent and Trademark Appeals, the CCPA stated:

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. . . . And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous. *In re Papesch*, 137 USPQ 43 (CCPA 1963).

None of the references, alone or in combination, teach **soluble** *Clostridium botulinum* toxin Type B and E fusion proteins. Applicants note that the specification makes a distinction

between soluble proteins and solubilized proteins. A soluble protein is a protein which is not found in an inclusion body inside the host cell or is found both in the cytoplasm and in inclusion bodies. *See* Specification, p. 19, lines 7-27. A solubilized protein is one found in an inclusion body which is solubilized by treating the purified inclusion bodies with denaturants such as guanidine hydrochloride, urea, or sodium dodecyl sulfate.

Therefore, it is not enough for the Examiner to argue that Ford *et al.*, "set forth that while many foreign proteins expressed intracellularly at high levels in *E. coli* and yeasts are produced as insoluble aggregates, often called refractile or inclusion bodies, these aggregates may be solubilized by using chaotropic agents such as guanidine hydrochloride or urea, and then removing the chaotropic agent to permit protein refolding." Office Action, page 4. In light of the distinction in the specification between soluble and solulizable, Ford *et al.* does not provide the missing element of **soluble** *Clostridium botulinum* toxin Type B and E fusion proteins.

Applicants note that the courts allow evidentiary showings of unexpected or superior properties between compounds. Thus, Applicants submit that because a compound and its properties are inseparable, the Examiner cannot pick and choose properties of structurally unrelated compounds (*i.e.*, fusions with different proteins) and claim that all the elements or properties of claimed compound are provided. The Examiner has apparently decided to conveniently leave out references disclosing *Clostridium botulinum* fusion proteins because those fusion proteins lack the property of being soluble.[1] This defect cannot be cured by citing references demonstrating that different, unrelated compounds are soluble or solubilizable. These compounds and their properties are completely unrelated structurally to the **soluble** *Clostridium botulinum* toxin Type B and E fusion proteins. When a skilled artisan considers references teaching clostridial proteins, it is clear that the prior art teaches clostridial fusion proteins are not soluble.

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[1] *See* LePenotier *et al.*, Development of a Molecular Engineered Vaccine for C. botulinum Neurotoxins, in Botulinum and Tetanus neurotoxins, B. R. DasGupta (Ed.), Plenum Press, New York, p. 463-466, (previously made of record) which discloses insoluble maltose binding protein-*Clostridium botulinum* type A toxin C fusion proteins.

In summary, the cited references do not teach **soluble** *Clostridium botulinum* toxin Type B and E fusion proteins. Therefore, the Examiner has not established a *prima facie* case of obviousness and the Claims should be passed to allowance.

C. Cited References do not Provide Reasonable Expectation of Success

The cited references do not provide a reasonable expectation of success for the claimed method. The Federal Circuit has held that "obvious to experiment" is not the standard for obviousness. *In re Dow Chemical*, 5 USPQ2d 1529, at 1532 (Fed. Cir. 1988). The *Dow* court made it very clear that one must determine whether "the prior art would have suggested to one of ordinary skill in the art that this process **should** be carried out and **would** have a reasonable likelihood of success, viewed in light of the prior art." *Id.* at 1531 (Emphasis added).

The Examiner states "[K]lied is cited as demonstrating success in producing fusion protein vaccines." Office Action, pg. 4. Applicants respectfully submit that the Examiner has inappropriately applied an "obvious to try" standard to the reasonable expectation of success element. As detailed above, the Claims are drawn to **soluble** *Clostridium botulinum* toxin Type B and E fusion proteins. The Kleid reference offers no guidance as to whether soluble *Clostridium botulinum* toxin Type B and E fusion proteins **would** be produced. The discovery of **soluble** *Clostridium botulinum* toxin Type B and E fusion proteins required a great deal of empirical experimentation that is explained in Dr. Williams Declaration, submitted 4/15/99, paragraph 14 (attached hereto as Tab 2 for the Examiner's convenience). Therefore, it appears that the Examiner has applied the impermissible "obvious to try" standard. Accordingly, Claims 10-14 and 25-28 are not obvious and should be passed to allowance.

D. *Prima Facie* case of Obviousness is Rebutted by Williams Declaration

A factually supported declaration by one skilled in the art must be considered by the Examiner.[2] Applicants submit that the Examiner has failed to consider Dr. Williams' Declaration. In his declaration, Dr. Williams states that the vaccines recited in independent

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[2] *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

amended Claim 10 have two unexpected properties, namely **solubility** and **neutralizing** activity, in view of the cited prior art.

1. Solubility was Unexpected

With respect to the unexpected solubility of the claimed vaccines, Dr. Williams' declaration explains that such solubility was unexpected since (a) the prior art, as exemplified by La Penotier *et al.*, taught that a fusion protein of *Clostridium botulinum* type A toxin C fragment and maltose binding protein (MBP) was **insoluble**, thus suggesting that other fusion proteins containing at least a portion of *Clostridium botulinum* type B and/or type E toxins would also be insoluble (Williams' declaration, paragraph 11), (b) Dr. Williams' preliminary experimental work which demonstrated the **insolubility** of two *Clostridium botulinum* fusion proteins, one of which falls within the scope of independent amended Claim 10 (Williams' declaration, paragraph 12) and (c) the **solubility** of the claimed vaccines was arrived at empirically rather than on the basis of the cited prior art's disclosure (Williams' declaration, paragraphs 12 and 17).

2. Neutralizing Activity was Unexpected

As to the unexpected neutralizing activity of the claimed vaccines, Dr. Williams' declaration establishes that this activity was surprising because (a) the prior art, as exemplified by Kleid, taught that generation of neutralizing antibodies was not *ipso facto* expected as a result of the mere generation of a fusion protein (Williams' declaration, paragraph 13), (b) the prior art, as exemplified by Acheson *et al.*, taught that antibodies against a toxin protein are not necessarily neutralizing (Williams' declaration, paragraph 14), (c) Dr. Williams' experimental work which failed to generate neutralizing antibodies with either soluble or insoluble toxins derived from *Staphylococcus aureus* and from *Clostridium difficile* (Dr. Williams' declaration, paragraph 15), and (d) the neutralizing activity of the claimed vaccines was arrived at empirically and not on the basis of the cited prior art (Williams' declaration, paragraphs 16 and 17).

As described above, under the rule of *In re Papesch*, a compound and its properties are inseparable, and unexpected properties of a compound must be given weight in determining patentability. The Declaration clearly shows that fusion proteins with unexpected properties (*i.e.*, solubility and neutralizing activity) were produced. The Examiner must consider the Declaration in light of *In re Papesch*. By showing unexpected properties, Dr.

William's declaration rebuts a *prima facie* case of obviousness (if such a case were arguably made by the Examiner). Accordingly, it is respectfully requested that the rejection of 10-14 and 25-28 under 35 U.S.C. § 103 be withdrawn.

3. The Declaration is Commensurate with the Scope of the Claims

The Examiner states that the Declaration is not commensurate in scope with Claim 10, which recites "a vaccine comprising" because the presence of Type A toxin cannot be excluded since its presence is encompassed by use of the term "comprising." Office ACtion, page 4. Applicants respectfully submit that rather than looking to what elements may be included in the claim, the Examiner should focus on whether the cited references teach elements which are actually recited in the claims. Elements which are not recited in the claims are irrelevant for obviousness purposes. Nonetheless, without waiving the argument above, and without acquiescing to the Examiner's arguments, Applicants submit new claims 29-31 which specify that the composition "consists" of fusion proteins consisting of either Type B or Type E toxins.

II. Claim 14 is Definite.

Claim 14 stands rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. The Examiner argues that Claim 14 is "vague and indefinite in the recitation of 'substantially' endotoxin free." Office Action, page 6. Applicants respectfully disagree with the Examiner's characterization of "substantially endotoxin-free" as indefinite because it is defined in the specification and because the term is understandable by those skilled in the art.

Applicants note "substantially endotoxin-free" is defined in the Specification at page 22, lines 2-3, as "[c]ompositions containing less than or equal to 250 endotoxin units (EU)/mg of purified recombinant protein . . . ." Therefore, the term is definite as used in Claim 14.

Furthermore, the Federal Circuit has held that the use of such modifiers as "substantially" does not render claims indefinite. The Federal Circuit summarized the relevant case law in *Andrew Corp. v. Gabriel Electronics*, 6 USPQ2d 2010, 2012 (Fed. Cir. 1988). In reversing the trial court's holding of invalidity on the ground that the claim expressions "approach each other," "close to," "substantially," and "closely approximate" were too vague to satisfy the requirement for definiteness, the Court said:

> The criticized words are ubiquitous in patent claims. Such usages, when serving reasonably to describe the claimed subject matter to those of skill in the field of the invention, and to distinguish the claimed subject matter from the prior art, have been accepted in patent examination and upheld by the courts. *Id.*

Applicants submit that, given the definition in the Specification, the subject matter of the Claim 14 is reasonably described to those of skill in the art. The definition and case law directly refute the Examiner's statement that "one of skill in the art would be able unable to determine the metes and bounds of the claimed limitation." Office Action, page 6. Therefore, the indefiniteness rejection should be withdrawn from Claim 14, and the Claim passed to allowance.

III. Applicants Reassert Their Prior Arguments

The Examiner has reasserted his previous arguments that: 1) Applicants are allegedly attempting to show non-obviousness by attacking references individually; and 2) that Applicants arguments that type A toxin is not recited in Claim 10 are not commensurate in scope with claim 10. Applicants have addressed these issues in detail in the Amendment and Response dated 4/15/99, and reasserts those arguments herein.

Indeed, as argued in Applicant's previous response, there can be no motivation to combine because: 1) the existence of a method for making a compound is irrelevant to the obviousness of the composition; 2) the Examiner does not indicate why an artisan would be motivated to make Claim 10's fusion protein by combining LeClerc *et al.*'s hepatitis or poliovirus fusion protein with the teaching of any other reference; and 3) there is no explanation why the mere disclosure of Kleid's fusion protein (a structural protein of hoof-and-mouth disease virus fused to peptide encoded by *the E. coli* tryptophan operon) motivates combining Kleid with any other reference to teach the fusion proteins of Claim 10.

Conclusion

All grounds of rejection and objection of the Office Action of June 8, 1999 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Examiner is encouraged to call Peter G. Carroll collect at (617) 252-3353.

Dated: September 8, 1999

Peter G. Carroll
Registration No. 32,837

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104
415.705.8410

APPENDIX I
PENDING CLAIMS AS AMENDED IN THIS COMMUNICATION

10. (Twice Amended) A soluble and neutralizing vaccine comprising a fusion protein, said fusion protein comprising a non-toxin protein sequence and at least a portion of one or more *Clostridium botulinum* toxins, said one or more toxins selected from the group consisting of type B toxin and type E toxin.

11. (Once Amended) The soluble and neutralizing vaccine of Claim 10 further comprising a fusion protein comprising a non-toxin protein sequence and at least a portion of *Clostridium botulinum* type A toxin.

12. (Once amended) The soluble and neutralizing vaccine of Claim 10, wherein said portion of said *Clostridium botulinum* toxin comprises the receptor binding domain.

13. (Once amended) The soluble and neutralizing vaccine of Claim 10 wherein said non-toxin protein sequence comprises a poly-histidine tract.

14. (Once amended) The soluble and neutralizing vaccine of Claim 10, wherein said vaccine is substantially endotoxin-free.

25. (Once Amended) The soluble and neutralizing vaccine of Claim 10, wherein said vaccine is protective against a challenge with said one or more *Clostridium botulinum* toxins.

26. (Once amended) The soluble and neutralizing vaccine of Claim 11, wherein said vaccine is protective against a challenge with said *Clostridium botulinum* type A toxin.

27. (Once amended) The soluble and neutralizing vaccine of Claim 10, wherein said portion of *Clostridium botulinum* type B toxin is selected from the group consisting of

SEQ ID NO:44 and SEQ ID NO:46, and said portion of *Clostridium botulinum* type E toxin is selected from the group consisting of SEQ ID NO:54 and SEQ ID NO:56.

28. (Once amended) The soluble and neutralizing vaccine of Claim 11, wherein said portion of *Clostridium botulinum* type A toxin is selected from the group consisting of SEQ ID NO:26 and SEQ ID NO:36.

29. (New) A soluble and neutralizing composition consisting of a fusion protein, said fusion protein comprising a non-toxin protein sequence and at least a portion of a *Clostridium botulinum* toxin is selected from the group consisting of Type B toxin and Type E toxin.

30. (New) The composition of Claim 29, wherein said non-toxin protein sequence comprises a poly-histidine tract.

31. (New) The composition of Claim 29, wherein said vaccine is substantially endotoxin-free.